

Long-Term Prostaglandin E₁ Therapy in Congenital Heart Defects

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Seventeen neonates received an intravenous infusion of prostaglandin E₁ for an average of 39 days (range 8 to 104). Seven (group 1) had transposition of the great arteries with no ventricular septal defect or a small one; eight (group 2) had ductus-dependent pulmonary flow (pulmonary atresia or stenosis in six and tricuspid atresia in two); and two (group 3) had aortic coarctation, one with no ventricular septal defect, the other with ventricular septal defect, isthmus hypoplasia and descending aortic flow supplied mainly by the ductus.

An increase in the arterial partial pressure of oxygen (PO₂) was seen in groups 1 and 2. Six patients from group 1 and two from group 2 developed heart failure; cortical

hyperostosis of long bones was seen in three patients from group 1 and three from group 2; one from group 1 had refractory diarrhea. Other side effects seen at the beginning improved as the rate of infusion diminished. In group 3, the patient with complex coarctation had a decrease in blood pressure in the arms, an increase in pressure in the legs and restoration of renal function; in the patient with no ventricular septal defect, heart failure worsened during therapy. Histologic changes seen in three ductus were attributed to the closing process.

When delaying surgery in selected ill infants with heart defects is deemed advantageous, long-term infusions of prostaglandin E₁ are feasible.

Type E prostaglandins have become a major advance in the management of neonates with certain critical heart defects (1-10). Their administration to maintain ductus arteriosus patency has been, in general, restricted to short periods (1-8). Although the short-term use in the newborn period appears to be well established, the experience with the prolonged use has been limited and the indications for therapy unclear (9-17). Our experience with the prolonged infusion of prostaglandin E₁ (Upjohn Company) in infants with congenital heart defects is presented in this report.

Methods

Patients. The study group comprised the 17 neonates who were treated with prostaglandin E₁ for a mean duration of 39 days (range 8 to 104) at our hospital from September 1979 to April 1983 (Table 1). Seven patients (group 1) had transposition of the great arteries and intact ventricular septum or small septal defect; eight patients (group 2) had

ductus-dependent pulmonary blood flow (pulmonary atresia or critical stenosis in six and tricuspid atresia in two); and two patients (group 3) had aortic coarctation, one with intact ventricular septum, the other with septal defect, isthmus hypoplasia and blood flow to the descending aorta supplied mainly by the ductus arteriosus.

Prostaglandin infusions. The prostaglandin infusion was maintained whenever it proved beneficial and it was deemed advantageous to delay surgical therapy beyond neonatal age. It was discontinued when no hemodynamic improvement could be proven, when there were persistent side effects (cortical hyperostosis) or when successful surgery was accomplished.

Prostaglandin E₁ was given intravenously at an initial rate of 0.05 µg/kg per min or less, and subsequently decreased to the lowest effective dose. In six patients from group 1, the infusion was started after cardiac catheterization because a satisfactory arterial oxygenation was not achieved after balloon septostomy; in one patient, the infusion was started before ballooning. In group 2, prostaglandin E₁ was started as soon as ductus-dependent pulmonary blood flow was suspected, even before confirmatory cardiac catheterization. In group 3, the infusion was started after catheterization.

Clinical and laboratory data. Arterial blood gases, blood pressure, temperature, heart rate and respiratory rate deter-

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Table 1. Clinical Summary

| Patient | Diagnosis | Prostaglandin E ₁ Infusion | | | Complications | Surgery | Outcome |
|--|-------------------------------|---------------------------------------|----------------------|-----------------|---|--|---------------------------------|
| | | Age at Beginning (days) | Dose (μg/kg per min) | Duration (days) | | | |
| Group 1: Patients With Transposition | | | | | | | |
| 1 | TGA, IVS | 1 | 0.05 | 19 | Heart failure | Blalock-Hanlon at 31 days | Well at 3 years |
| 2 | TGA, IVS | 1 | 0.05 | 44 | Heart failure, hypotension, pyrexia, seizure, diarrhea | Blalock-Hanlon at 40 days | Mustard procedure at 11 mo |
| 3 | TGA, small VSD | 1 | 0.05 | 8 | Heart failure, pyrexia | Senning at 10 mo | Well at 3 years |
| 4 | TGA, IVS | 1 | 0.05–0.01 | 65 | Heart failure, pyrexia, diarrhea, cortical hyperostosis | Senning at 66 days | Died postoperatively at 66 days |
| 5 | TGA, IVS | 1 | 0.05–0.00625 | 50 | Heart failure, pyrexia, seizure, cortical hyperostosis | Blalock-Hanlon at 31 days, aortopulmonary shunt at 50 days | Died postoperatively at 50 days |
| 6 | TGA, small VSD | 6 | 0.05–0.009 | 20 | Apnea, bradycardia | | Well at 6 mo |
| 7 | TGA, IVS | 1 | 0.05–0.015 | 104 | Heart failure, pyrexia, cortical hyperostosis | Blalock-Hanlon at 99 days | Well at 5 mo |
| Group 2: Patients With Ductus-Dependent Pulmonary Blood Flow | | | | | | | |
| 8 | LTGA, VSD, P Atr | 2 | 0.05 | 42 | Hypotension, rash, tachycardia, tachypnea, bradycardia | Aortopulmonary shunt at 44 days | Died postshunt revision at 2 mo |
| 9 | P Atr, IVS | 3 | 0.05 | 11 | Pyrexia, seizure | Pulmonary valvotomy at 9 days | Well at 3 years |
| 10 | P Atr, IVS, hypopl RV | 1 | 0.05 | 14 | Heart failure, seizure | Pulmonary valvotomy at 14 days | Died intraoperatively |
| 11 | T Atr, VSD, hypopl RV | 1 | 0.05–0.0125 | 20 | Pyrexia, tachypnea | Aortopulmonary shunt at 7 days | Well at 2 years |
| 12 | P Atr, VSD | 1 | 0.05–0.0125 | 40 | Hypotension, seizure | Aortopulmonary shunt at 5, 26 and 40 days | Well at 1 year |
| 13 | ToF | 23 | 0.05–0.02 | 45 | Rash, cortical hyperostosis | Aortopulmonary shunt at 97 days | Well at 8 mo |
| 14 | TGA, T Atr, P Atr, VSD | 1 | 0.05–0.0125 | 35 | Tachypnea, tachycardia | Aortopulmonary shunt at 35 days | Died postoperatively |
| 15 | TGA, Mitral Atr, SV, PS | 1 | 0.05–0.0125 | 64 | Heart failure, pyrexia, apnea, bradycardia, cortical hyperostosis | Blalock-Hanlon at 27 days, aortopulmonary shunt at 61 days | Well at 4 mo |
| Group 3: Patients With Aortic Coarctation | | | | | | | |
| 16 | Ao coarc, VSD, isthmic hypopl | 4 | 0.017–0.009 | 38 | Tachypnea | Ao angioplasty, PA band, PDA ligation at 38 days | Died postoperatively |
| 17 | Ao coarc, IVS | 11 | 0.05 | 9 | Heart failure, pyrexia, seizure | | Died suddenly at 33 days |

Ao = aortic; Atr = atresia; coarc = coarctation; hypopl = hypoplasia; IVS = intact ventricular septum; LTGA = levotransposition of the great arteries; P = pulmonary; PA = pulmonary artery; PDA = patent ductus arteriosus; PS = pulmonary stenosis; RV = right ventricle; SV = single ventricle; T = tricuspid; ToF = tetralogy of Fallot; TGA = transposition of the great arteries; VSD = ventricular septal defect.

minations were obtained before the infusion, within 1 hour and every 4 hours; blood gases were measured weekly thereafter. Serum glucose and electrolytes, blood urea nitrogen or creatinine, hemoglobin, hematocrit, white cell and platelet counts were monitored at least weekly. Body weight and urine output were measured daily. Any adverse reaction was recorded.

Results

Group 1: transposition of great arteries. In these patients, the arterial partial pressure of oxygen (PO_2) increased from a mean preinfusion level of 27 torr (range 22 to 32) to a mean postinfusion level of 40 torr (range 31 to 48) that was elevated for the remainder of the therapy. The efficacy of prostaglandin E₁ was tested by occasional interruption of the infusion followed by a decrease in the arterial oxygen tension (Fig. 1).

Cardiomegaly and cardiac failure developed in six patients but promptly responded to medical treatment. Symmetric cortical hyperostosis of long bones was seen in three patients after 22, 25 and 84 days, respectively. The patients were irritable and had tenderness and swelling in the limbs. Typical radiologic appearance is seen in Figure 2. One patient had refractory diarrhea requiring total parenteral nutrition for 34 days. There were other side effects seen at the beginning of the treatment similar to those reported previously (9,18). Seizure-like activity was seen in two patients, pyrexia in five and hypotension and mild diarrhea in one.

Blalock-Hanlon atrial septectomy was performed in four patients. In one, the infusion was necessary even after the septectomy; an aortopulmonary anastomosis was performed on the 50th day of prostaglandin E₁ therapy but the child did not survive surgery. Another patient underwent a modified Senning procedure on the 66th day of infusion and died on the first postoperative day. At autopsy, the ductus was 20 mm long and 9 mm wide; its internal diameter was 6 mm. The midportion had been surgically ligated. Microscopically, fibrinous deposits were seen on the endothelial surface; the intimal cushions were normal; the internal elas-

tic layer was thin and large interruptions were seen at the level of the intimal cushions; the media showed clear spaces consistent with edema and no inner medial necrosis or fibrosis.

Group 2: ductus-dependent pulmonary blood flow. In these patients a sharp increase in arterial PO_2 to a mean level of 48 torr (range 39 to 56) from the pretreatment level of 30 torr (range 22 to 37) was observed (Fig. 3). Adequate systemic arterial tension was maintained up to 64 days. In only two patients was cardiac decompensation seen. In two patients, mild cortical hyperostosis was detected radiologically on days 39 and 58, respectively. Side effects seen at the beginning were pyrexia in three patients, hypotension in two, apnea in one, rash in one, tachypnea in three, tachycardia and bradycardia in two and seizure-like activity in three.

Two patients (Cases 9 and 10) underwent pulmonary valvotomy, one dying at surgery. An aortopulmonary shunt was performed in six patients, two of whom died; the surgery was performed twice in both patients because of thrombus formation in the prosthetic tubing. Thrombosis was immediate in one (Case 14), and delayed in the other (Case 8). At autopsy, in Case 8 the ductus was 20 mm long, 3 mm wide externally and 1 mm wide internally; the lumen was covered by fibrinous material; the intimal cushions were thickened, fibrosed and circumferential; and the elastica was wavy with focal areas of fragmentation and duplication in contact with the intimal cushion but there was no interruption. No fibrosis or necrosis of the inner media or edema of the outer media was noted.

Group 3: aortic coarctation (Fig. 4). In this group, the patient (Case 16) with complex coarctation (near arch interruption) had a decrease in blood pressure in the upper limbs, an increase in blood pressure in the legs and restoration of renal function while the infusion persisted. The infusion was stopped on the 38th day when subclavian flap angioplasty, pulmonary artery banding and ductus ligation were done. In the patient with an intact ventricular septum (Case 17), heart failure worsened and only cleared when the prostaglandin infusion was stopped, and marked systemic hypertension unresponsive to medical treatment fol-

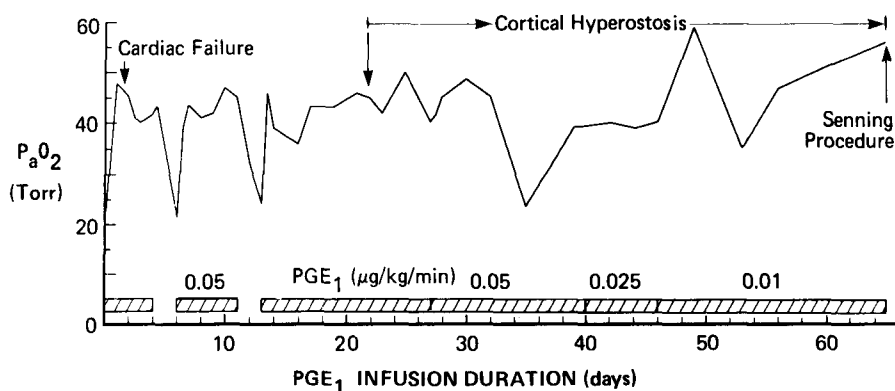


Figure 1. Patient 4. An increase in the arterial PO_2 (P_{aO_2}) is accompanied by cardiomegaly and cardiac failure. A decrease in PO_2 occurs after occasional interruptions of the prostaglandin E₁ (PGE_1) infusion. Symmetric cortical hyperostosis of long bones of the limbs was seen on day 22.



Figure 2. Patient 7. **A**, Upper limb radiograph on day 98 showing considerable periosteal new bone formation along the humerus, radius and ulna. Similar changes were seen in the other arm and both lower limbs, and to a much lesser extent in the clavicles and ribs. **B**, Upper limb radiographs 3 months after prostaglandin E₁ therapy had been discontinued. Note considerable regression of the periosteal lesions, equally observed in the lower limbs.

lowed. He died suddenly 2 weeks after prostaglandin E₁ had been discontinued. Postmortem examination revealed a patent ductus 11 mm long with an external diameter of 6 mm and an internal diameter of 2 mm. Microscopically, the intimal cushions were thickened, deformed and fibrosed, and fibrinous deposits were noted on the surface; the internal elastic layer was wavy with focal fragmentation and dupli-

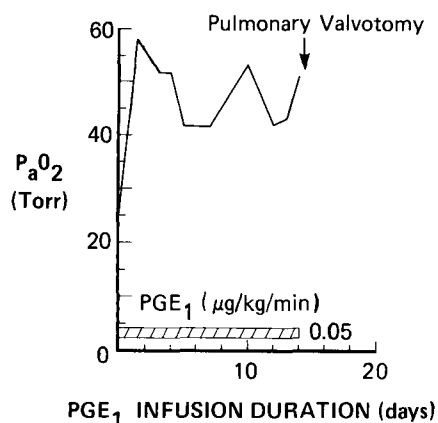
cation, and areas of interruption were noted in contact with the intimal cushion; the inner media showed focal necrosis and fibrosis in continuity with the intimal cushion fibrosis at the level of the interrupted elastica; and there was edema of the outer media.

Discussion

Morphologic changes in ductus after prolonged prostaglandin infusion. The long-term effectiveness of prostaglandin E₁ in maintaining ductus patency has been demonstrated previously (11,12,16,17-21). However, the fear of adverse effects may restrict its administration to short periods of time.

Potentially dangerous changes in the structure of the ductus have been attributed to prolonged use of prostaglandin E₁. Cole et al. (17) described the ductus in an infant after 39 days of prostaglandin E₁ therapy. It showed disruption of the internal elastic lamella; localized increase in the medial elastic tissue; areas of disarray and destruction of medial muscular fibers; medial elastic fragmentation, edema and cavitation; thickening and mononuclear cell infiltration of the adventitia at the ductus-pulmonary artery junction, the infiltration extending to the nerve trunks, which also displayed edema and cavitation; and generalized increase of

Figure 3. Patient 10. Adequate arterial PO₂ (P_aO₂) is maintained with prostaglandin E₁ infusion (PGE₁).



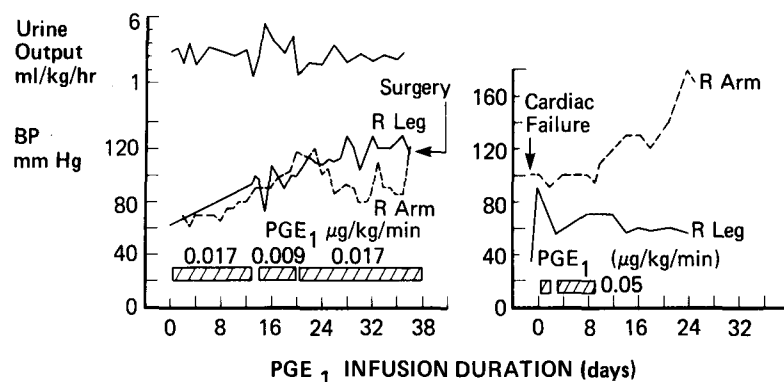


Figure 4. Patients 16 (left) and 17 (right). A decrease in systolic blood pressure (BP) in the upper limbs and an increase in the lower limbs is produced by prostaglandin E₁ (PGE₁) infusion. This relation reverted whenever the infusion was interrupted. Changes in urinary output (top left) seen in Patient 16 correspond to manipulation of the infusion. Cardiac failure was aggravated in Patient 17, improving when the therapy was stopped. R = right.

mucopolysaccharides. Gittenberger-de Groot et al. (22) reported the histologic findings in four ductus after infusion of prostaglandin E₁ for 10 hours to 3 days. These consisted of medial edema and separation by clear spaces, interruptions of the internal elastic lamina and intimal lacerations, sometimes extending into the media.

In an extensive study to define the normal structure of the closing ductus, Silver et al. (23) examined 103 specimens from fetuses and newborn infants of different gestational ages, birth weights and diagnoses, including 17 with congenital heart defects who received prostaglandin E₁ over a period of 4 to 7 days. The lesions found in prostaglandin E₁-treated and nontreated babies consisted of intimal fibrinous deposits, focal hemorrhages and dissecting aneurysms of differing degrees. Each of these lesions occurred in all groups with the exception of stillborns, who failed to show intimal fibrinous deposits or focal hemorrhages, and infants older than 3 weeks, who did not show dissecting aneurysms. No morphologic differences could be seen between the three types of lesions in the prostaglandin E₁-treated and nontreated patients of the same age. The investigators concluded that the lesions were due not necessarily to the prostaglandin E₁ therapy, but to the ductus patency for whatever reason.

In three of our patients, the ductus was examined histologically. The changes found were: 1) intimal cushion thickening and fibrosis in two; 2) internal elastic fragmentation and duplication in two, and interruption in one; and 3) medial edema, necrosis and fibrosis at the cushion level in two. These changes are also found in the normally closed ductus (23) and were not attributed to the prostaglandin therapy. No lacerations, hemorrhage or aneurysms that could predispose to ductal rupture were found. Similarly, Park et al. (24) found no significant deleterious morphologic changes after prostaglandin E₁ infusion.

Symmetric laminar cortical hyperostosis of long bones of the limbs. This adverse effect was seen in five patients, accompanied by swelling and tenderness in three and detected radiologically only in two. This phenomenon, not previously reported from North America, has been seen in Japan in association with long-term infusion of low dose

prostaglandin E₁ (13,21). These changes in the limbs resemble those of Caffey's disease, but the conspicuous absence of involvement of the mandible, the minimal or no involvement of the clavicles and the symmetry of the lesions are in sharp contrast with this disease. Prostaglandins of the E series are potent local mediators of bone resorption; furthermore, prostaglandin synthesis is necessary for the production of osteoclast-activating factor by normal human peripheral blood leukocytes (25). The stimulation of bone resorption by the E prostaglandins varies in a bell-shaped way as the prostaglandin concentration increases (26). As suggested by Dekel and Francis (27), it is possible that the same prostaglandin at a higher concentration stimulates bone formation. Why the local effects are more prevalent in the long bones of the limbs is uncertain.

Other side effects. These occurred at the beginning of therapy and lessened when the rate of infusion was decreased. These adverse reactions may also occur during short-term therapy, and have been reported previously elsewhere (9-18). Heart failure due to the prolonged added ductus flow was seen in some of our patients. Although in patients with transposition or ductus-dependent pulmonary blood flow, heart failure was easily managed medically or with a decrease in the prostaglandin E₁ infusion, in patients with simple coarctation improvement was only achieved after the infusion was discontinued.

Conclusions. The ductus responsiveness to prostaglandin E₁ persists for many weeks. Adverse effects are seen mostly at the beginning of the therapy, are dose-related and reverse promptly when the treatment is stopped or the dose is decreased. Symmetric cortical hyperostosis of long bones may be seen after 3 weeks of therapy. It also appears to be dose-related, taking longer to manifest when smaller doses are used. It reverses spontaneously, clinically and radiologically, when the treatment is discontinued. Morphologic changes observed in the ductus are likely related to the normal closing process, not to the use of prostaglandin. When it is deemed advantageous to delay surgery in selected critically ill infants with congenital heart defects, long-term infusions of prostaglandin E₁ are feasible.

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